

DBL™ FLUCLOXACILLIN SODIUM POWDER FOR INJECTION

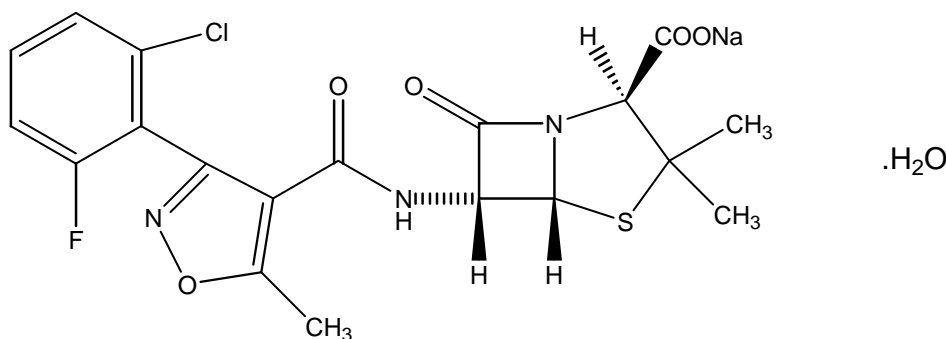
NAME OF THE MEDICINE

Flucloxacillin sodium

DESCRIPTION

DBL™ Flucloxacillin Sodium Powder for Injection is the sodium salt of flucloxacillin. Flucloxacillin is 3-(2'-chloro-6'-fluorophenyl)-5-methyl-4-isoxazoly]penicillin monohydrate. It is a member of the beta-lactamase-stable group of penicillins derived from the penicillin nucleus, 6-amino-penicillanic acid. Flucloxacillin is closely related to cloxacillin.

The chemical formula of flucloxacillin sodium is C₁₉H₁₆ClFN₃NaO₅S.H₂O. Its molecular weight is 493.9 and its CAS registry number is 1847-24-1. The chemical structure of flucloxacillin sodium is shown below:



Flucloxacillin sodium is a white or almost white, crystalline powder, hygroscopic, freely soluble in water and in methanol, soluble in alcohol.

DBL™ Flucloxacillin Sodium Powder for Injection contains 1 g of flucloxacillin as flucloxacillin sodium.

PHARMACOLOGY

Microbiological

Flucloxacillin is a narrow spectrum antibiotic with considerable activity against the following common Gram-positive organisms:

- Beta-lactamase-producing *Staphylococcus aureus*
- Penicillin sensitive *Staphylococcus aureus*
- Beta-haemolytic streptococci (*Streptococcus pyogenes*)
- Streptococcus pneumoniae* (*Diplococcus pneumoniae*)

It is not active against Gram-negative bacilli, methicillin resistant *Staphylococcus aureus*, nor *Streptococcus faecalis*.

Pharmacokinetic properties

Absorption: Flucloxacillin is stable in acid media and can therefore be administered either by the oral or parenteral route. The peak serum levels of flucloxacillin reached after 1 hour are as follows.

- After 500 mg by the I.M. route: approximately 16.5 mg/L.

- After 250 mg by the oral route (in fasting subjects): approximately 8.8 mg/L.
- After 500 mg by the oral route (in fasting subjects): approximately 14.5 mg/L.

The total quantity absorbed by the oral route represents approximately 79% of the quantity administered.

DBL™ Flucloxacillin Sodium Powder for Injection is well absorbed following intramuscular administration.

Distribution: Flucloxacillin diffuses well into most tissues. Specifically, active concentrations of flucloxacillin have been recovered in bones: 11.6 mg/L (compact bone) and 15.6 mg/L (spongy bone), with a mean serum level of 8.9 mg/L.

Crossing the meningeal barrier: flucloxacillin diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed.

Crossing into mother's milk: flucloxacillin is excreted in small quantities in mother's milk.

Metabolism: In normal subjects approximately 10% of the flucloxacillin administered is metabolized to penicilloic acid. The elimination half-life of flucloxacillin is on the order of 53 minutes.

Excretion: The major route of excretion is renal (by both glomerular filtration and tubular secretion) and high levels of active antibiotic are produced in the urine. Between 65.5% (oral route) and 76.1% (parenteral route) of the dose administered is recovered in unaltered active form in the urine within 8 hours. A small portion of the dose administered is excreted in the bile. The excretion of flucloxacillin is slowed in cases of renal failure.

The concurrent administration of probenecid delays the excretion of DBL™ Flucloxacillin Sodium Powder for Injection resulting in higher and more prolonged blood levels of the antibiotic.

Protein Binding: Flucloxacillin, in common with other isoxazolympenicillins, is highly bound to serum proteins. The low MICs of flucloxacillin against Gram-positive cocci and the free antibiotic levels achieved however ensure that the preparation is fully active against susceptible pathogens.

INDICATIONS

For the treatment of confirmed or suspected staphylococcal and other Gram-positive coccal infections. Indications include pneumonia, osteomyelitis and skin and skin structure infections, such as wound infections, infected burns and cellulitis.

CONTRAINDICATIONS

Patients with a previous history of flucloxacillin associated jaundice or hepatic dysfunction.

DBL™ Flucloxacillin Sodium Powder for Injection should not be given to patients with a history of hypersensitivity to beta-lactam antibiotics (eg penicillins, cephalosporins).

DBL™ Flucloxacillin Sodium Powder for Injection should not be used in the eye, either conjunctively or locally.

PRECAUTIONS

WARNING

Liver Toxicity

Flucloxacillin can cause severe hepatitis and cholestatic jaundice, which may be protracted. This reaction is more frequent in older patients and those who take the drug for prolonged periods (see ADVERSE EFFECTS).

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY REACTIONS (ANAPHYLAXIS) HAVE BEEN REPORTED IN PATIENTS RECEIVING BETA-LACTAM ANTIBIOTICS. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL THERAPY. BEFORE COMMENCING THERAPY WITH ANY BETA-LACTAM ANTIBIOTIC, CAREFUL ENQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, APPROPRIATE THERAPY SHOULD BE INSTITUTED AND FLUCLOXACILLIN THERAPY DISCONTINUED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE EMERGENCY TREATMENT WITH ADRENALINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including flucloxacillin. A toxin produced with *Clostridium difficile*, appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Hepatitis, predominantly of a cholestatic type, has been reported (see **ADVERSE EFFECTS**). Reports have been more frequent with increasing age (particularly over 55 years of age) or following prolonged treatment (more than 14 days). Jaundice may appear several weeks after therapy: in some cases the course of the reactions has been protracted and lasted for several months. Resolution has occurred with time in most cases. In rare cases, deaths have been reported, nearly always in patients with serious underlying disease or receiving concomitant medication.

Animal studies show that high doses of flucloxacillin reduce albumin bound bilirubin to 50 to 70% of the base line concentration. The drug should therefore be used with extreme caution in jaundiced neonates or premature infants.

During prolonged treatment it is advisable to check periodically for hepatic dysfunction in patients with impaired hepatic function.

The dose or dose interval may need modification in patients with renal failure as the half life in patients with renal failure is increased. As renal function is not fully developed in the neonate the risk/benefit ration should be considered before administration to such patients.

Caution should be exercised in the treatment of patients with an allergic diathesis.

It should be recognised that each 1 gram of flucloxacillin sodium contains 2.2 mmol of sodium.

Use in pregnancy: Category B1

Animal studies with flucloxacillin have shown no teratogenic effects. The product has been in clinical use since 1970 and the limited number of reported cases of use in human pregnancy have shown no evidence of untoward effect. The use of DBL™ Flucloxacillin Sodium Powder for Injection in pregnancy should be reserved for cases considered essential by the clinician.

Australian categorisation definition of:

Category B1: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.*

Studies in animals have not shown evidence of an increased occurrence of foetal damage.

Use in lactation

Flucloxacillin is excreted in breast milk in trace amounts. An alternative feeding method is recommended to avoid any possible sensitisation of the newborn.

Interactions with other medicines

Probenecid decreases the renal tubular secretion of flucloxacillin. Concurrent use with DBL™ Flucloxacillin Sodium Powder for Injection may result in increased and prolonged blood levels of flucloxacillin.

It is recommended that DBL™ Flucloxacillin Sodium Powder for Injection and aminoglycosides not be mixed together in the same solution for injection due to possible precipitation and the gradual inactivation of the aminoglycosides under these circumstances.

DBL™ Flucloxacillin Sodium Powder for Injection injections should not be mixed with blood products or other proteinaceous fluids (e.g. protein hydrolysates).

ADVERSE EFFECTS

The following adverse reactions have been reported as associated with the use of flucloxacillin.

Hepatic: Hepatitis and cholestatic jaundice (occasionally severe) have been reported with a frequency of about 1 in 15 000 exposures (see **PRECAUTIONS**).

Gastrointestinal: Nausea, vomiting, diarrhoea, dyspepsia, constipation, abdominal pain, heart burn, loss of appetite. As with other antibiotics, pseudomembranous colitis has been reported rarely (see **PRECAUTIONS**).

Hypersensitivity reactions: Erythematous maculopapular rashes, urticaria, purpura, eosinophilia, angioneurotic oedema, erythema nodosum. Anaphylaxis and erythema multiforme have been reported rarely. Certain reactions (fever, arthralgia and myalgia) sometimes develop more than 48 hours after the start of treatment. Whenever such reactions occur, DBL™ Flucloxacillin Sodium Powder for Injection should be discontinued. (Note: Urticaria, other skin rashes and serum sickness like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids).

Renal: Isolated cases of nephritis, frequency of micturation and haematuria have been reported. Interstitial nephritis may occur but is reversible when treatment is discontinued.

Pulmonary: Bronchospasm.

Haemic and lymphatic systems: Haemolytic anaemia has been reported during therapy with flucloxacillin. Reactions such as anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leucopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Neurological effects: In patients suffering from renal failure, neurological disorders with convulsions are possible with the I.V. injection of high doses.

Other: Malaise, bad taste, sore throat, sore tongue, pruritus vulvae, arthralgia, dizziness, depression and headache.

DOSAGE AND ADMINISTRATION

Usual adult dosage

Intramuscular	250 mg 6 hourly
Intravenous	250 mg to 1 g 6 hourly
Intrapleural	250 mg once daily
Intra-articular	250 mg to 500 mg once daily

Note : Systemic doses may be doubled where necessary in severe infections.

Usual children's dosage

2 to 10 years	1/2 adult dose
under 2 years	1/4 adult dose

Note : In severe infections the dosage may be increased.

Dosage in patients with impaired liver function

Adjustment of dosage may not be necessary as flucloxacillin is not metabolised in the liver to any appreciable extent. However, during prolonged treatment it is advisable to check periodically for hepatic dysfunction.

Dosage in patients with impaired renal function

As flucloxacillin is excreted to a large extent by the kidney, the dose or dose interval may need modification in patients with renal failure, as the half life in patients with renal failure is increased. However dosage recommendations for various plasma creatinine levels for patients with impaired renal function are not available. Flucloxacillin is not significantly removed by haemodialysis.

Directions for use

Intramuscular: Dissolve 1 g vial content in 2.5 mL Water for Injections BP.

Intravenous: Dissolve 1 g in 15 to 20 mL Water for Injections BP. Administer by slow IV injection (3 to 4 minutes).

DBL™ Flucloxacillin Sodium Powder for Injection may also be added to infusion fluids or injected, suitably diluted, into the drip tube over a period of 3 to 4 minutes.

Stability in solution

All injections should be reconstituted from the injection presentations under appropriate aseptic conditions and the solutions prepared should be used as soon as practicable after preparation to reduce microbiological hazards. If storage is necessary, hold at 2 to 8°C for not more than 24 hours. The solutions should be used in one patient on one occasion only and any residue discarded as the solutions do not contain an antimicrobial preservative.

Solutions of flucloxacillin in water for injections (500 mg/mL), 0.5% lignocaine hydrochloride solution (500 mg/mL), 0.9% sodium chloride solution (1 mg/mL), 2.5% glucose in 0.45% sodium chloride solution (1 mg/mL), 5% glucose in water (1 mg/mL) and 1/6 M sodium lactate solution (1 mg/mL) have been shown to be stable for 24 hours when stored at 2 to 8°C.

OVERDOSE

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically.

Flucloxacillin is not removed from the circulation by haemodialysis.

PRESENTATION AND STORAGE CONDITIONS

Vials containing flucloxacillin sodium equivalent to 1.0 g of flucloxacillin in cartons of 5.

DBL™ Flucloxacillin Sodium Powder for Injection should be stored in a dry place at less than 25°C.
Protect from light and moisture.

NAME AND ADDRESS OF THE SPONSOR

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MEDICINE CLASSIFICATION

Prescription Only Medicine

DATE OF PREPARATION

18 January 2012